PATENT
ATTORNEY DOCKET NO.: 00786/246002

Certificate of Mailing: Date of Deposit: September 2, 2003

I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Guy E. Beardsley
Printed name of person mailing correspondence

Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	David Moore et al.	Art Unit:	1646
Serial No.:	09/365,576	Examiner:	M. Pak
Filed:	August 2, 1999	Customer No.:	21559
Title:	RETINOID X RECEPTOR-INTERACTING POLYPEPTIDES AND RELATED MOLECULES AND METHODS		

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANTS' SECOND BRIEF ON APPEAL SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

In support of Appellants' Notice of Appeal that was filed in the above-captioned case on October 23, 2002 of the Office's final rejection mailed on April 23, 2002, and with reference to the Advisory Action mailed on June 30, 2003, submitted herewith in triplicate is Appellants' Second Brief on Appeal. Appellants note that this brief is being filed to address the issues raised in the June 30, 2003 advisory action, mailed after appellants filed its Appeal Brief on March 24, 2003.

TABLE OF CONTENTS

Table of Cases

Real Party in Interest

The real party in interest is The General Hospital Corporation, to whom all interest in the present application has been assigned (Reel 010520, Frame 0605).

Related Appeals and Interferences

There are no currently pending appeals or interferences related to this case.

Status of Claims

Claims 7, 10, 13-16, and 27-31 are currently pending.

Claims 7, 10, 13-16, and 27-31 were finally rejected in an Office Action mailed on April 23, 2002 and are appealed.

Claims 1-6, 8, 9, 11, 12, and 17-26 stand pending but withdrawn from consideration.

Status of Amendments

The amendments up to and including the Amendment of December 28, 2001 have been entered. In its Advisory Action mailed June 30, 2003, the Office denied entry of appellants' Amendment filed October 23, 2002 in reply to the final Office Action mailed on April 23, 2002. This amendment canceled claims 1-6, 8, 9, 11, 12, and 17-26 and added claim 32, which recites RXR-interacting proteins that inhibit retinoid X receptor-

dependent activation of a β-RARE-linked nucleic acid (as disclosed, for example, on page 40, lines 8 to 19). Appellants request reconsideration of entry of this Amendment.

Summary of the Invention

Appellants have discovered a novel protein, termed RIP15 (see, for example, page 14, lines 12-20, and Figure 5). RIP15 specifically interacts with the retinoid X receptor (RXR) and binds β-retinoic acid response elements (β-RAREs) (pages 16, lines 5-17, and page 24, lines 7-24).

Issues

This appeal presents four issues:

1. Whether the Office erred in objecting to claim 37 for being drawn to a non-elected invention.

2. Whether the Office erred in rejecting claims 7, 10, 13-16, and 27-31 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, for lack of utility.

3. Whether the Office erred in rejecting claims 7, 10, 13, 14, 16, 27, 28, and 31 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description.

4. And whether the Office erred in rejecting claims 7, 10, 13, 14, 16, 27, 28, and 31 under 35 U.S.C. § 102(e), as being anticipated by Liao *et al.* (U.S.P.N. 5,639,616).

Grouping of Claims

Due to the number of issues raised on appeal, the claims do not stand or fall together. In particular, the claims are grouped as follows: claims 7, 10, 13-16, 27, 28, 31, and 32 in Group I and claims 29 and 30 in Group II. This separation is based on the rejections applied to each group of claims. While claims 29 and 30 are rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph for lack of utility, there can be no question that the claimed proteins, which have an amino sequence that is 100% identical to the sequence of RIP15 disclosed in the specification, are novel and adequately described by their specific amino acid sequence. Indeed, claims 29 and 30 are free of the prior art and written description rejections.

Arguments

As is clear from the Issues section above, one or more of the pending claims stand rejected on the grounds of utility, enablement, and novelty. Each of these rejections, as applied in the Office actions and Advisory Action, is now presented.

I. The Objection to Claim 37 Should Be Reversed

Claim 37 was objected to for being drawn to a non-elected invention. As the application contains only claims 1-31, this objection should be reversed.

II. The Utility Rejection Should Be Reversed

Claims 7, 10, 13-16, and 27-31 were finally rejected under 35 U.S.C. § 101 and § 112, first paragraph, with the Office stating that the claimed invention is not supported by a substantial or specific asserted utility or by a well established utility that would enable one skilled in the art to use the invention. This rejection is in error and should be reversed.

A. Standards for Satisfying the Utility Requirement

The Utility Examination Guidelines (66 CFR 1092-1099) and Revised Interim Utility Guidelines Training Materials outline the criteria to determine the utility of an invention. The utility of an invention must be specific and substantial or well-established. In defining the metes and bounds of a specific utility, the Revised Interim Utility Guidelines Training Materials require that:

> a utility [be] specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention ... A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed (paragraph bridging pages 5 and 6; emphasis added).

By implication, therefore, the specific utility of a particular protein may be established by the disclosure of a specific disease or condition with which it is associated.

Likewise, a substantial utility is established by a "real world" context of use, such as the identification of a material which has a correlation to, or impacts the onset or

progression of a particular disease or condition. Specifically, the Revised Interim Utility Guidelines state:

> both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring (page 6; emphasis added).

Thus, a component of an assay method for identifying candidate compounds which may be used for treating a specific disease itself has substantial utility. Similarly, components of an assay method for measuring the presence of a material associated with a risk of disease have substantial utility.

Alternatively, the utility requirement of 35 U.S.C. § 101 can also be satisfied by identifying a well established utility which is defined in the Revised Interim Utility Guidelines Training Materials as:

> A specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art (page 7; emphasis added).

Of course, in evaluating the utility of the invention, the credibility of the disclosure must be assessed. Credibility must be viewed from the perspective of a person of ordinary skill in the art and should be based on the totality of the evidence (specification and prior art) and reasoning provided.

The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) has articulated the standard to be applied by the PTO in any challenge to an assertion of utility. In this case, the court stated:

> the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. [citation omitted]. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility (page 1566; emphasis added).

The Office has failed to carry this burden. As discussed below, Appellants have asserted the specific and substantial utilities of using RIP15 (i) to inhibit RXR function in a subject for the treatment of an RXR-associated disease, such as hyperthyroidism, (ii) to identify a compound that increases RIP15 expression as a treatment for an RXR-associated disease (e.g., hyperthyroidism), and (iii) to generate an anti-RIP15 antibody for the detection or monitoring of an RXR-associated disease (e.g., hyperthyroidism). Further, the Office has presented no credible evidence that would cause a person of ordinary skill to doubt the asserted utilities of the present invention. On these bases, this rejection should be reversed.

B. Specific Functions of RIP15

The present invention is based on Appellants' discovery of a novel receptor, RIP15, that interacts with the retinoid X receptor (RXR). The specificity of the interaction of RIP15 with RXR is demonstrated by the lack of interaction between RIP15 and other nuclear receptors, such as TR, RAR, MB67, and GR (page 16, Table 1).

Additionally, heterodimers of RIP15 and RXR bind DNA specifically. In particular, RIP15 binds a β-RARE (β-retinoic acid response element) in the presence of RXR. Moreover, Appellants discovered that RIP15 completely blocks RXR-dependent transcription of a reporter gene linked to a β-RARE in a mammalian cell-based assay (page 24, lines 7 to 24, and Figure 9). Thus, Appellants' specification demonstrates several important facts about RIP15 specificity that are the basis for Appellants' asserted utilities.

C. RIP15 Has Therapeutic Utility for the Treatment of RXR-Associated Diseases

The disclosed ability of RIP15 to eliminate RXR-dependent activation of β-RARE linked genes strongly supports the specific utility of RIP15, analogs of RIP15, and fragments of RIP15 as therapeutics for the inhibition of RXR function in a subject (page 40, lines 8 to 19, and page 42). As stated on page 2, lines 14-24, of the specification:

> members of the RXR family play important roles in several aspects of development and central nervous system differentiation as well as in adult physiology. Based on both their specific response to the 9-cis-RA metabolite and their heterodimerization with the RARs, it is clear that the RXRs play a central role in the broad regulatory effects of retinoids. Moreover, their heterodimeric interactions with other family members indicate that the RXRs also play a central role in response to thyroid hormone, vitamin D, and perhaps other compounds.

From this disclosure, a skilled artisan would clearly understand that inhibiting RXR function is desirable for the treatment of diseases associated with an elevated level of hormone (*e.g.*, thyroid hormone, retinoic acid, or vitamin D) or hormone-mediated activity. For example, hyperthyroidism is caused by the production of excess thyroid

hormone, and thus hyperthyroidism can be treated by inhibiting the body's response to thyroid hormone. Because RXR is required for full hormone-dependent transcriptional activity of the thyroid hormone receptor-RXR complex, administration of RIP15 to a subject with hyperthyroidism would be expected to reduce the adverse effects caused by the excess thyroid hormone and the resulting excess thyroid hormone receptor activity (page 2, lines 4-6).

Appellants note that these asserted disease associations are neither general in nature, nor are they inconsistent with what one skilled in the art would expect for the specific disease involvement of RIP15 based on Appellants' disclosure of its ability to inhibit RXR function. Thus, Appellants have asserted a specific, substantial, and credible utility with a "real world" context for RIP15 proteins.

D. Compounds that Increase RIP15 Expression Have Utility as Therapeutics for the Treatment of RXR-Associated Diseases

In addition to direct therapeutic use, RIP15 can also be used in standard methods to identify compounds that increase or decrease its expression and therefore its interaction with RXR (see, for example, page 34, line 28 through page 35, line 12). One skilled in the art would appreciate that compounds that increase RIP15 expression are also useful for the treatment of diseases associated with an elevated level of hormone or hormone-mediated activity (e.g., hyperthyroidism). Again, the asserted utility of identifying compounds for the treatment of hyperthyroidism satisfies the criteria for a specific and substantial utility. The credibility of this utility is strongly supported by the

disclosed "central role in response to thyroid hormone" of RXR and the reasonable conclusion that inhibiting RXR function is desirable for the treatment of diseases associated with elevated thyroid hormone levels or activity (page 2, line 23).

E. An Anti-RIP15 Antibody Has Utility for the Detection or Monitoring of RXR-Associated Diseases

RIP15 can also be used for the generation of anti-RIP15 antibodies for the detection or monitoring of RXR-related diseases (see, for example, page 40, line 20 through page 41, line 12). For example, anti-RIP15 antibodies can be used to detect decreased levels of RIP15, which are likely associated with increased risk or severity of RXR-associated diseases such as hyperthyroidism. Again, the credibility of this specific and substantial utility is supported by Appellants' discovery of the ability of RIP15 to inhibit RXR function and the reasonable association of decreased RIP15 levels with increased RXR function. A skilled artisan would appreciate the high level of predictability between this increased RXR function and increased risk or severity of RXR-associated diseases such as hyperthyroidism. As the Office is aware, a compound (e.g., RIP15 protein) which enables the production of a useful end product (e.g., an anti-RIP15 antibody) is itself patentably useful under 35 U.S.C. § 101. *In re Kirk*, 376 F.2d 936 (C.C.P.A. 1967).

F. RIP15 Has Utility for Purifying or Isolating β-RARE or β-RARE-Linked Nucleic Acids

In addition to the above three utilities, the specification also clearly conveys that RIP15 is able to bind a β-RARE, a known and useful material. For example, Sucov *et al.* (U.S.P.N. 5,091,518, a copy of which is enclosed) reports that β-RAREs can be used to enhance transcriptional activity of promoters (abstract; column 1, lines 10-17; and column 2, lines 26-35). In particular, a β-RARE can be added to a vector encoding a protein of interest to generate an "enhanced expression system" that is responsive to retinoic acid (column 5, lines 48-50 and column 8, lines 30-41).

The binding of RIP15 to β-RAREs allows RIP15 to be used to purify or isolate β-RAREs or β-RARE-linked nucleic acids. This utility would also have been apparent to one skilled in the art reading the specification, as binding of a β-RARE by RIP15 is discussed in the specification on pages 21 and 22. The use of RIP15 to isolate a β-RARE is sufficient to satisfy § 101. As noted above, RIP15 protein, which enables the production of a useful end product (e.g., purified β-RARE), is itself patentably useful under 35 U.S.C. § 101. *In re Kirk*, 376 F.2d 936 (C.C.P.A. 1967).[1]

G. Four Credible, Specific, and Substantial Utilities Have Been Asserted

The analysis to be carried out in making a rejection under 35 U.S.C. § 101 must include a determination of whether an assertion of utility has been made in an Appellants'

[1] The Office is also reminded that a patent is presumed valid under 35 U.S.C. § 282. Accordingly, one may presume that the utility disclosed in Sucov for the claimed β-RAREs is a valid, credible utility.

specification and, if so, whether that asserted utility is credible (*i.e.*, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided; M.P.E.P. § 2107.01-III(B)).

In the present case, Appellants have asserted the utilities described above. Appellants submit that, absent data to the contrary, it is credible that administration of RIP15 protein or a compound that increases RIP15 expression will ameliorate RXR-associated conditions, and further that detection of decreased RIP15 levels in a subject using an anti-RIP15 antibody will identity subjects at increased risk for these conditions. Nonetheless, while the Office has stated that these utilities are not credible, no evidence has been provided that may be relied upon to reach this conclusion, as the Guidelines require. In particular, the Guidelines state that the Office

> must treat as true any statement of fact made by the Applicant in relation to the asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement... [I]t is improper to disregard the opinion [of a qualified expert] solely because of a disagreement over the significance or meaning of the facts offered. (M.P.E.P. § 2107, emphasis added)

To be properly rejected under § 101, the Guidelines set forth that a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result," *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992), as cited in the Legal Analysis accompanying the Utility Examination Guidelines (M.P.E.P. § 2107.01-II). The only instances in which the federal courts have found a lack of patentable utility were where, "based upon the factual record

of the case, it was clear that the invention could and did not work as the inventor claimed it did" (M.P.E.P. § 2107.01-II, emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art" (M.P.E.P. § 2107.02-IIIB).

Procedurally, the M.P.E.P. makes clear that the burden is on the Office to provide a detailed, reasoned explanation for the rejection that is supported, if possible, by documentary evidence indicating why the asserted utility is more likely than not "incredible." "An applicant's assertion of utility creates a presumption of utility" (M.P.E.P. § 2107.01-III(A)); "Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being 'wrong,' even when there may be reason to believe that the assertion is not entirely accurate" (M.P.E.P. § 2107.01-III(B)). Conversely, if the Office determines that the claimed invention has a credible utility, neither a 35 U.S.C. § 101 nor a related 35 U.S.C. § 112 rejection may be applied (or, upon rebuttal of the Office's position, both rejections must be simultaneously reversed).

In the present case, Appellants assert four utilities in the specification, that are, on their face, credible. Appellants assert that the present invention provides RIP15 protein that can be used directly as a therapeutic, used to identify potential therapeutics that lead to decreased RXR activity, or used to generate diagnostic anti-RIP15 antibodies whereas,

prior to the present invention, this was not possible because RIP15 was unavailable and its function was not known. At least some of the identified compounds that increase RIP15 expression are expected to have the proposed therapeutic activity of treating a RXR-associated disease (particularly hyperthyroidism). Additionally, one skilled in their art would appreciate that RIP15's ability to bind a β-RARE enables RIP15 to be used for the isolation or purification of a β-RARE from, for example, synthetic DNA libraries, genomic libraries, or cell lysates. No evidence has been made of record to dispute any of these utilities, and on this basis alone the rejection should be reversed.

H. RIP15 Ligand is not Required for Asserted Utilities

In addition, contrary to the position taken by the Office, Appellants note that none of the four asserted utilities presented above require the identification of a ligand for RIP15. In particular, RIP15 and polypeptides derived from RIP15 can be tested for their ability to inhibit RXR in the cell-based assay described in Appellants' specification on pages 23 and 24 or in any animal model of disease without the use of a ligand for RIP15. A RIP15 ligand is also not needed to identify therapeutic compounds that modulate RIP15 expression, to generate anti-RIP15 antibodies for diagnostic applications, or to purify a β-RARE. The basis for the rejection should be reversed.

I. Summary

In sum, given the uses of RIP15 based on Appellants' demonstration of the ability of RIP15 to interact with and inhibit RXR or to bind β-RAREs, the related rejections under 35 U.S.C. § 101 and § 112, first paragraph should be reversed. It is noted that all assertions must be shown to be incredible for this rejection to stand. It is Appellants' understanding that the Office will either provide a rebuttal for each of Appellants' assertions of utility or will reverse these rejections in view of the clarifications which have been provided during prosecution.

III. The Written Description Rejection Should Be Reversed

Claims 7, 10, 13-16, and 27-31 were also finally rejected under 35 U.S.C. § 112, first paragraph, for lack of a written description. This rejection should be reversed.

Independent claim 7 requires a substantially pure RXR-interacting protein that includes an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3). The other pending independent claim, claim 27, requires an RXR-interacting protein produced by expression of a purified DNA encoding a protein that includes an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3). Claims 10 and 28 require 90% identity and 95% identity, respectively, to SEQ ID NO: 3, and claims 29 and 30 require 100% identity to SEQ ID NO: 3.

As an initial matter, Appellants point out that, with respect to claims 29 and 30,

there can be no question that the written description requirement is satisfied, as SEQ ID NO: 3 is presented in Appellants' specification.

With respect to the remaining claims, the rejection turns on the assertion that the "essential feature" of the claimed invention is the RIP15 sequence of SEQ ID NO: 3. This rejection should be reversed.

Appellants assert that 100% identity to the RIP15 sequence of SEQ ID NO: 3 is not essential to the present invention. In defining the term "RXR-interacting protein," the specification clearly teaches that proteins with at least 85% identity to RIP15 can also interact with RXR:

> By "RXR-interacting protein" is meant a polypeptide which directly or indirectly physically interacts with a retinoid X receptor in the in vivo protein interaction assay described herein.... Preferably, such a polypeptide has an amino acid sequence which is at least 85%, preferably 90%, and most preferably 95% or even 99% identical to the amino acid sequence of an interacting protein described herein (e.g., RIP14, RIP15, RIP110, or RIP13) at the point of interaction with the retinoid X receptor, or [is] at least 80% and preferably 90% identical overall.

(Page 5, line 24 through page 6, line 5).

The specification further describes mutations that can be made to the RIP15 sequence to maintain the ability of the protein to interact with RXR. For example, page 6, line 26 through page 7, line 5 of the specification states:

> By "substantially identical" is meant an amino acid sequence which differs only by conservative amino acid substitutions, for example, substitution of one amino acid for another of the same class (e.g., valine for glycine, arginine for lysine, etc.) or by one or more non-conservative substitutions, deletions, or insertions located at positions of the amino acid sequence which do not destroy the function of the protein (assayed, e.g., as described herein). Preferably, such a sequence is at least 85%, more preferably 90%, and most preferably 95% identical

at the amino acid level to one of the sequences of Figs. 4, 5, 10, and 11 (SEQ ID NOS: 1-5).

Standard methods, such as those described on pages 41-43, can be used to generate proteins with at least 85% sequence identity to the disclosed sequence of RIP15 (SEQ ID NO: 3). These proteins are structurally characterized by this high level of sequence identity to SEQ ID NO: 3. As 100% sequence identity to SEQ ID NO: 3 is not necessary for the claimed invention, Appellants respectfully assert that it would be unfair to limit the present claims to only those proteins with 100% sequence identity to SEQ ID NO: 3.

Appellants further assert that one skilled in the art would appreciate that the essential feature of the claimed invention is the ability of the claimed proteins to interact with RXR. For example, page 3, line 30 through page 4, line 5 of the specification states:

> In a second aspect, the invention features a substantially pure preparation of a retinoid X receptor (RXR)-interacting protein. Preferably, the RXR-interacting protein is RIP14, RIP15, RIP110, or RIP13; or includes an amino acid sequence substantially identical to an amino acid sequence shown in any of Figs. 4, 5, 10, and 11 (SEQ ID NOS: 1-5); is derived from a mammal, for example, a human; binds a β-RARE site in the presence of RXR; or binds an EcRE site in the presence of RXR.

Appellants note that all of the pending claims, through the definition of "RXR-interacting protein," include the functional limitation that the protein interacts with RXR. Appellants further note that the *in vivo* interaction trap assay described in the specification can readily be used by one skilled in the art to determine whether a protein with at least 85% sequence identity to the sequence of RIP15 (SEQ ID NO: 3) interacts with RXR (see, for example, pages 11-14). Alternatively, a skilled artisan can easily

determine whether the protein interacts with RXR by determining whether the protein inhibits RXR-dependent activation of a β-RARE-linked nucleic acid (as disclosed, for example, on page 24, lines 7-24). Other standard methods for determining whether a protein interacts with RXR include gel filtration chromatography and co-immunoprecipitation assays.

In response to the Office's assertion that a functional limitation cannot be used to limit the claims because RIP15 is an orphan receptor, Appellants respectfully assert that further characterization of RIP15, such as identification of a ligand for RIP15, is not necessary to distinguish the claimed proteins from other proteins. As stated in the Written Description Guidelines (66 FR 1106),

> [f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

As noted above, the claimed proteins are distinguished from other proteins by both the structural characteristic of having at least 85% sequence identity to SEQ ID NO:3 and by the specific functional characteristic of interacting with RXR. In contrast, RIP15 does not bind other receptors, such as TR, RAR, MB67, and GR (page 16, Table 1). Additionally, Appellants note that the specification teaches other functional characteristics of RIP15. For example, RIP15 binds a β-RARE in the presence of RXR

(claim 15) and inhibits RXR-dependent activation of a β-RARE-linked nucleic acid (claim 32). Based on Appellants' disclosure of these properties and routine assays for determining whether a particular protein has these properties, one skilled in the art would appreciate that Appellants were in possession of the claimed invention.

As clear distinguishing characteristics that are shared by the claimed proteins are disclosed in Appellants' specification, this rejection should be reversed.

IV. The Novelty Rejection Should Be Reversed

Claims 7, 10, 13, 14, 16, 27, 28, and 31 were finally rejected under 35 U.S.C. § 102(e) as being anticipated by Liao *et al.* (U.S.P.N. 5,639,616), a patent stemming from a continuation-in-part application, the parent of which had a filing date of November 10, 1993. Accordingly, the earliest possible § 102(e) date for this reference is November 10, 1993.[2]

The Declaration of inventor Dr. David Moore, filed December 28, 2001, presented documentation that Appellants obtained an exemplary RIP15 cDNA sequence prior to November 10, 1993. Because the claimed invention was reduced to practice prior to the earliest filing date of Liao, Liao cannot constitute prior art to the present claims under 35 U.S.C. § 102(e).

This rejection should also be reversed.

---

2 Appellants note that, because this reference is continuation-in-part application, the actual § 102(e) date may actually be the filing date of the continuation-in-part application, November 18, 1994.

Appellants also note that the Office issued an Advisory Action on June 30, 2003. In its Advisory Action, the Office maintained the § 102(e) rejection as follows:

> In regard to the 102(e) rejection as being anticipated by Liao *et al.*, the Declaration of Dr. Moore filed December 28, 2001 does not overcome the rejection because applicant did not provide [a] showing under 37 C.F.R. 1.608(b). See MPEP 2308.02.

In a concurrently filed Petition (copy enclosed), appellants request that the final rejection of claims 7, 10, 13-16, and 27-31 as applied in the Advisory Action mailed June 30, 2003 be withdrawn. In particular, the Office, in both its first and final actions, had rejected the claims, under § 102(e), on the ground that "Liao et al. disclose ubiquitous nuclear receptor which is 97.1% identical to SEQ ID NO:3." The Office's requirement for a showing under 37 C.F.R. 1.608(b) was first raised in its Advisory Action mailed June 30, 2003. To properly raise this issue, the finality of the rejection must be withdrawn in order to apply the new ground of rejection concerning the showing under 37 C.F.R. 1.608(b).

Conclusion

Appellants respectfully request that the rejection of claims 7, 10, 13-16, and 27-31 be reversed and allowed. No fees are believed to be due at this time. If, however, there are any other charges, or any credits, in connection with filing this brief, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 2 September 2003

Karen L. Elbing, Ph.D.
Reg. No. 35,238

James D. DeCamp
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

Appendix of Claims on Appeal

1. (Withdrawn) A method for determining whether a test protein is capable of interacting with a retinoid X receptor (RXR) protein, comprising:

(a) providing a host cell which contains

(i) a reporter gene operably linked to a protein binding site;

(ii) a first fusion gene which expresses a first fusion protein, said first fusion protein comprising a retinoid X receptor protein covalently bonded to a binding moiety which is capable of specifically binding to said protein binding site; and

(iii) a second fusion gene which expresses a second fusion protein, said second fusion protein comprising said test protein covalently bonded to a gene activating moiety; and

(b) determining whether said test protein increases expression of said reporter gene as an indication of its ability to interact with said retinoid X receptor protein.

2. (Withdrawn) The method of claim 1, wherein said method further comprises treating said host cell with a ligand which binds said retinoid X receptor and identifying a ligand-dependent interacting protein by its ability to increase expression of said reporter gene upon treatment of said cell by said ligand.

3. (Withdrawn) The method of claim 1, wherein said method further comprises treating said host cell with a ligand which binds said retinoid X receptor and identifying a ligand-independent interacting protein by its ability to increase expression of said reporter gene both in the presence and in the absence of said ligand treatment.

4. (Withdrawn) The method of claim 1, wherein said method further comprises treating said host cell with a ligand which binds said retinoid X receptor and identifying a

ligand-sensitive interacting protein by its ability to increase expression of said reporter gene in the absence but not in the presence of said ligand treatment.

5. (Withdrawn) The method of claim 1, wherein said gene activating moiety is the gene activating moiety of B42.

6. (Withdrawn) The method of claim 2, wherein said ligand is 9-cis-RA.

7. (Previously presented) A substantially pure RXR-interacting protein, comprising an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

8. (Withdrawn) The protein of claim 7, comprising an amino acid sequence substantially identical to the amino acid sequence of RIP14-1 shown in Figure 4 (SEQ ID NO: 1).

9. (Withdrawn) The protein of claim 7, comprising an amino acid sequence substantially identical to the amino acid sequence of RIP14-2 shown in Figure 4 (SEQ ID NO: 2).

10. (Previously presented) The protein of claim 7, comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of RIP15 shown in Figure 5 (SEQ ID NO: 3).

11. (Withdrawn) The protein of claim 7, comprising an amino acid sequence substantially identical to the amino acid sequence of RIP110 shown in Figure 10 (SEQ ID NO: 4).

12. (Withdrawn) The protein of claim 7, comprising an amino acid sequence substantially identical to the amino acid sequence of RIP13 shown in Figure 11 (SEQ ID NO: 5).

13. (Previously presented) The protein of claim 7, wherein said protein is derived from a mammal.

14. (Original) The protein of claim 13, wherein said mammal is a human.

15. (Previously presented) The protein of claim 13, wherein said protein binds a β-retinoic acid response element (β-RARE) in the presence of RXR.

16. (Previously presented) The protein of claim 13, wherein said protein binds an ecdysone response element (EcRE) in the presence of RXR.

17. (Withdrawn) Purified DNA comprising a sequence encoding a protein of claim 7.

18. (Withdrawn) The purified DNA of claim 17, wherein said DNA encodes a human RXR-interacting protein.

19. (Withdrawn) The DNA of claim 17, comprising a DNA sequence substantially identical to the DNA sequence of RIP14-1 shown in Figure 4 (SEQ ID NO: 6).

20. (Withdrawn) The DNA of claim 17, comprising a DNA sequence substantially identical to the DNA sequence of RIP14-2 shown in Figure 4 (SEQ ID NO: 14).

21. (Withdrawn) The DNA of claim 17, comprising a DNA sequence substantially identical to the DNA sequence of RIP15 shown in Figure 5 (SEQ ID NO: 7).

22. (Withdrawn) The DNA of claim 17, comprising a DNA sequence substantially identical to the DNA sequence of RIP110 shown in Figure 10 (SEQ ID NO: 8).

23. (Withdrawn) The DNA of claim 17, comprising a DNA sequence substantially identical to the DNA sequence of RIP13 shown in Figure 11 (SEQ ID NO: 9).

24. (Withdrawn) A vector comprising the purified DNA of claim 17.

25. (Withdrawn) A cell containing the purified DNA of claim 17.

26. (Withdrawn) A method of producing a recombinant RXR-interacting protein comprising, providing a cell transformed with DNA encoding an RXR-interacting protein positioned for expression in said cell;

culturing said transformed cell under conditions for expressing said DNA; and

isolating said recombinant RXR-interacting protein.

27. (Previously presented) RXR-interacting protein produced by expression of a purified DNA encoding a protein comprising an amino acid sequence that is at least 85% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

28. (Previously presented) The protein of claim 7, comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

29. (Previously presented) The protein of claim 7, comprising an amino acid sequence that is identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

30. (Previously presented) The protein of claim 7, wherein the amino acid sequence of said protein is identical to the amino acid sequence of RIP15 (SEQ ID NO: 3).

31. (Previously presented) The protein of claim 7, said protein interacting with a retinoid X receptor in an *in vivo* interaction trap assay.